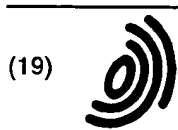


Good Data



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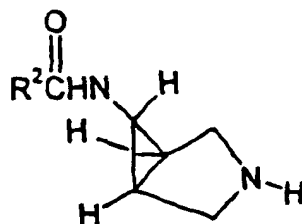
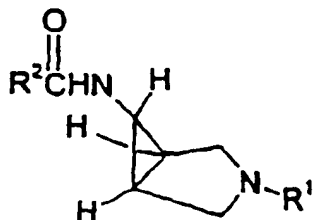
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(54) A process for preparing naphthyridones and intermediates

(57) A process for preparing a naphthyridone carboxylic acid and its derivatives makes use of side chain intermediates of formulae I and IV



IV

I

wherein

R¹ is benzyl, wherein the phenyl of the benzyl may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro amino or trifluoromethyl, and

R² is C₁-C₆ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl,

and process for preparing intermediate I.

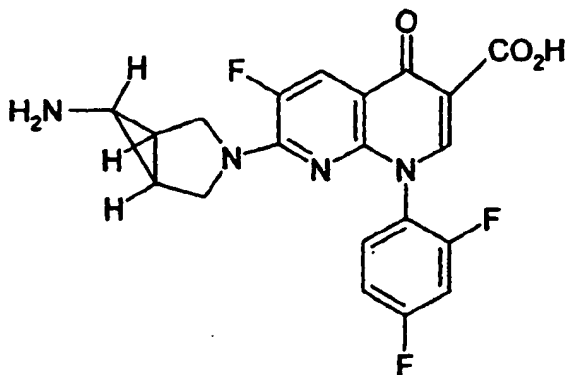
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Description

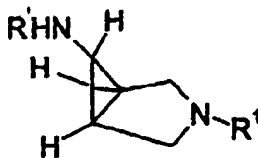
[0001] This invention relates to a process for preparing the naphthyridone carboxylic acid, trovafloxacin and derivatives thereof, and intermediates of use therein.

[0002] Trovafloxacin has the formula



VII

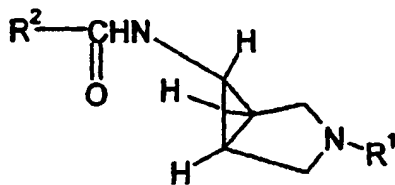
as disclosed in U.S. Patent No. 5,164,402. The patent also discloses processes for making the compound by using an intermediate of the formula



wherein R' is a nitrogen protecting group, such as tertiary butyloxycarbonyl.

[0003] U.S. Patent No. 5,475,116 discloses the preparation of other intermediates for use in preparing the naphthyridones of U.S. Patent No. 5,164,402.

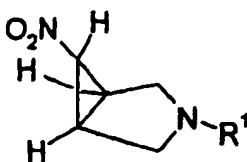
[0004] The present invention relates to a process for preparing a compound of the formula



I

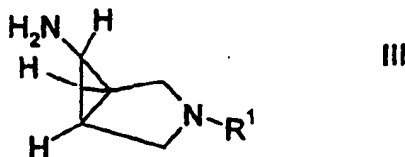
wherein R¹ is benzyl, wherein the phenyl of the benzyl may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, and R² is C₁-C₆ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, which comprises

(a) reducing a compound of the formula



II

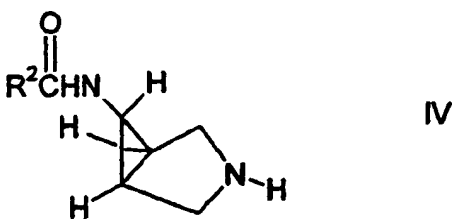
wherein R^1 is as defined above, in the presence of iron and a organic solvent under acidic conditions, and (b) acylating the compound of formula III formed:



10 with an acylating agent of the formula $R^2C(O)X$ wherein R^2 is as defined above, and X is a leaving group.

[0005] In a preferred embodiment of the invention, the compound of formula III formed in step (a) is not isolated before acylation step (b).

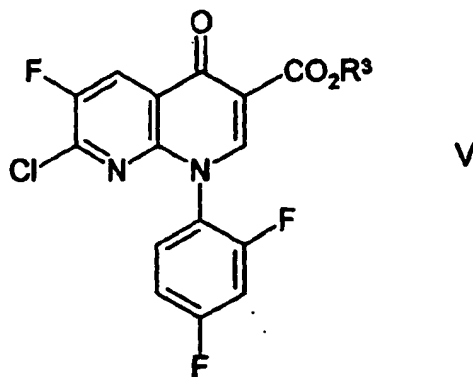
15 [0006] The invention is further related to a process for preparing a compound of the formula



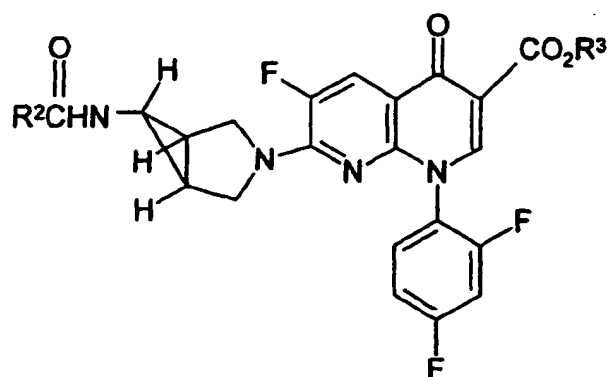
25 by debenzylating the compound of formula I wherein R^1 and R^2 are as defined above.

[0007] In a preferred embodiment, the debenzylation is carried out by reacting a compound of formula I with hydrogen and palladium catalyst in acetic acid and an organic solvent.

30 [0008] The invention also relates to reacting a compound of the formula IV with a compound of the formula



45 wherein R^3 is C_1 - C_6 alkyl, to form a compound of the formula

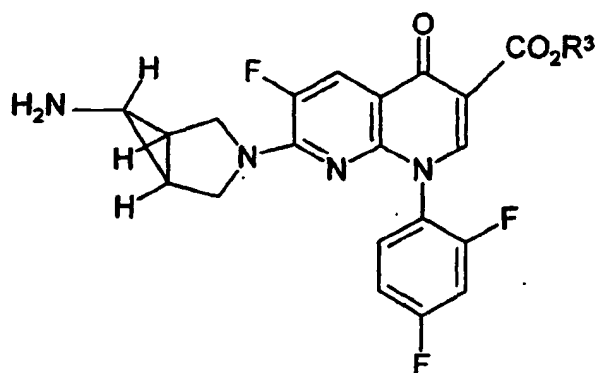


VI

wherein R² is as defined above with reference to formula I.

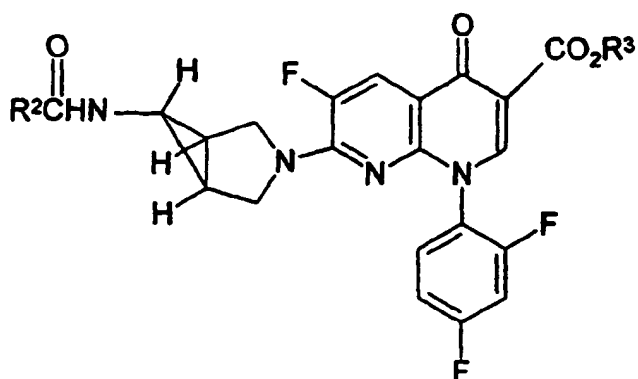
[0009] The invention relates to hydrolyzing the compound of formula VI with methanesulfonic acid, water and an organic solvent to form the monomethanesulfonic acid salt of the compound of the formula VII, trovafloxacin.

[0010] The invention also relates to hydrolysis of the compound of formula VI with methanesulfonic acid and R³OH wherein R³ is as defined above to form the monomethanesulfonic acid salt of the compound of the formula



VIII

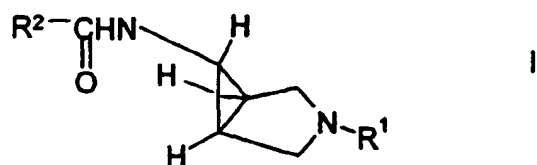
[0011] The invention further relates to the intermediates of the formulae



VI

wherein R² is C₁-C₆ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, and

R³ is C₁-C₆ alkyl,
and



wherein

R¹ is hydrogen (see formula IV) or benzyl, wherein the phenyl of the benzyl may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, and

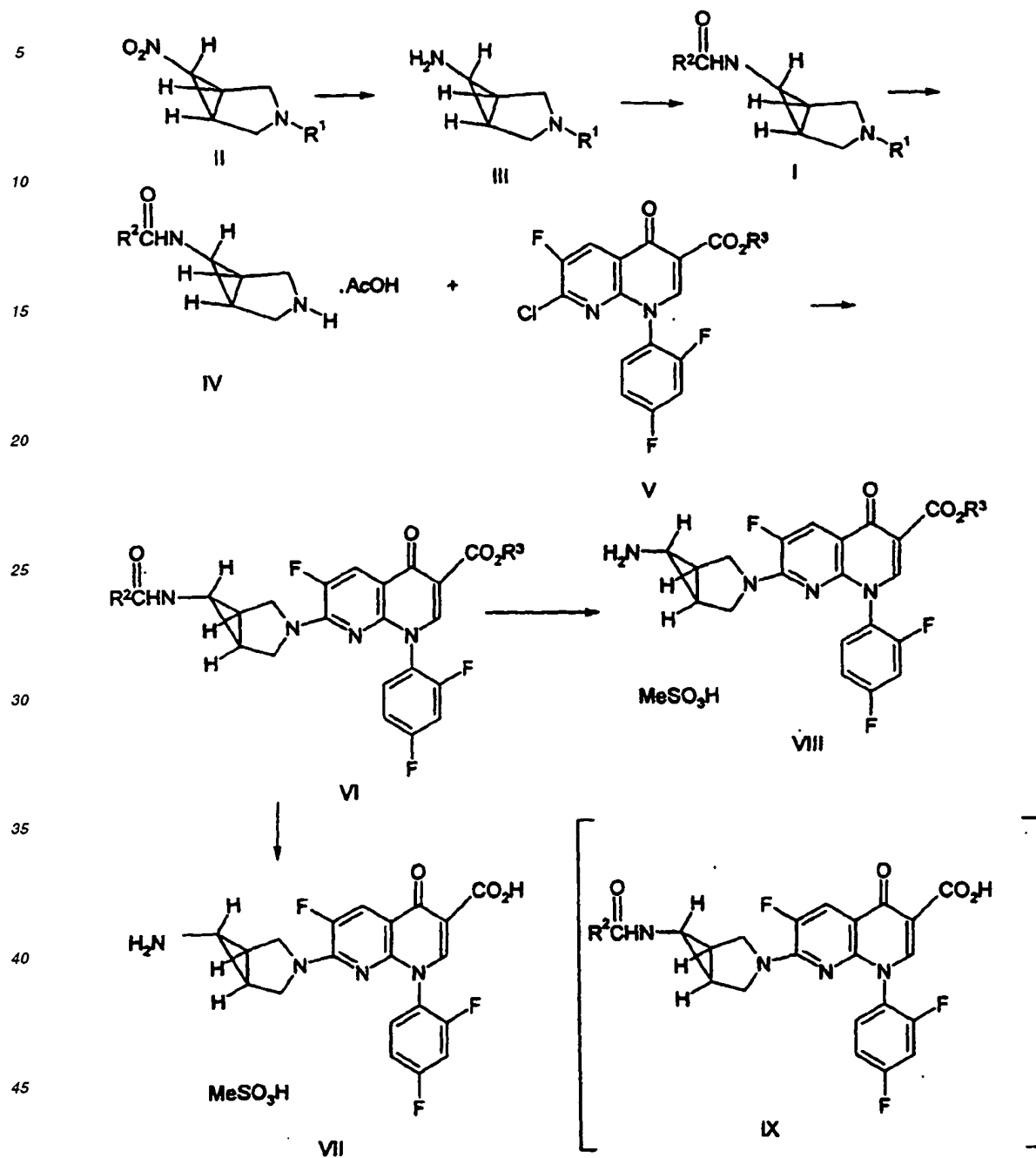
R² is C₁-C₆ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl.

[0012] The term "alkyl", as used herein, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties, e.g. methyl, ethyl.

[0013] The term "alkoxy", as used herein, includes O-alkyl groups wherein "alkyl" is defined above.

[0014] The processes of the invention are depicted in the following reaction scheme. Unless indicated otherwise, R¹, R², R³ and X are as defined above.

Reaction Scheme



[0015] The compound of formula III is prepared from the corresponding compound of formula II by reduction in the presence of iron and an organic solvent under acidic conditions. The organic solvent is a C₁-C₆ alcohol, such as ethanol, or an ether such as tetrahydrofuran (THF), and preferably, an alcohol. The acidic conditions are obtained by use of a mineral acid, such as hydrochloric acid, or an organic acid, such as acetic acid (AcOH). Acetic acid is preferred since it generally results in increased yields.

[0016] The compound of formula III may then be isolated from the reaction mixture or may be reacted further *in situ*, without isolation from the reaction mixture. In either case, the further processing is by acylation with an acylating agent of the formula R²C(O)X to form the compound of formula I. The leaving group X is conveniently a halogen, such as

chloro, or the acetoxy group. If the compound of formula III is first isolated, then the acylation may be conducted under conventional acylating conditions, for instance, in the presence of an organic solvent of the type discussed above.

[0017] The compound of formula I is subjected to debenzilation to form the compound of formula IV. It is understood that in the context of the invention, debenzilation includes removal of R¹ wherein R¹ is benzyl or substituted benzyl.

5 The reaction proceeds in accordance with conventional debenzilation of tertiary nitrogen, conveniently by use of hydrogen and palladium catalyst in acetic acid, and in an organic solvent. The organic solvent may be a C₁-C₆ alcoholic solvent, such as ethanol, ethyl acetate, THF or water, or a mixture thereof, such as ethanol and water.

[0018] The compound of formula VI is obtained by coupling the corresponding compound of formula IV with the bicyclic intermediate ester of formula V. This coupling reaction may be conducted with or without a solvent. The solvent, when used, must be inert under the reaction conditions. Suitable solvents are ethyl acetate, acetonitrile, tetrahydrofuran, ethanol, chloroform, dimethylsulfoxide, pyridine, and water, and mixtures thereof.

[0019] The reaction temperature usually ranges from about 20°C. to about 150°C.

[0020] The reaction may advantageously be carried out in the presence of an acid acceptor such as an inorganic or organic base, e.g. an alkali metal or alkaline earth metal carbonate or bicarbonate, or a tertiary amine, e.g. triethylamine, pyridine or picoline.

[0021] The mesylate salt of the compound of formula VII, trovafloxacin, is formed by hydrolysis of the compound of formula VI with methanesulfonic acid, water and an organic solvent. Examples of suitable organic solvents include a C₁-C₆ alcohol, acetone, dimethoxy ethane, glyme, THF, N-methyl-pyrrolidinone, and water, and mixtures thereof.

20 [0022] The mesylate salt of the compound of formula VIII is obtained by hydrolysis of the compound of formula VI with methanesulfonic acid and a C₁-C₆ alcohol of the formula R³OH, for example ethanol. The compound of formula VIII is an intermediate in the preparation of the mesylate salt of a prodrug of trovafloxacin wherein the amino group is substituted by an amino acid or a polypeptide, e.g. dipeptide, as disclosed in U.S. Patent No. 5,164,402.

[0023] The compound of formula IX in the Reaction Scheme is the intermediate formed in the reaction from compound VI to VII.

25 [0024] The compound of formula VII and the mesylate salt thereof (the active compounds) are useful in the treatment of bacterial infections of broad spectrum, particularly the treatment of gram-positive bacterial strains.

[0025] The active compounds may be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally or in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25-500 ppm. They can be injected parenterally, for example, intramuscularly, intravenously or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which can contain other solutes, for example, enough salt or glucose to make the solution isotonic.

35 In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1-50 mg/kg/day, advantageously 0.2-10 mg/kg/day given in a single daily dose or up to 3 divided doses.

[0026] The invention also provides pharmaceutical compositions comprising an antibacterially effective amount of a compound of the formula (I) together with a pharmaceutically acceptable diluent or carrier.

40 [0027] The compounds of the invention can be administered to humans for the treatment of bacterial diseases by either the oral or parenteral routes, and may be administered orally at dosage levels of about 0.1 to 500 mg/kg/day, advantageously 0.5-50 mg/kg/day given in a single dose or up to 3 divided doses. For intramuscular or intravenous administration, dosage levels are about 0.1-200 mg/kg/day, advantageously 0.5-50 mg/kg/day. While intramuscular administration may be a single dose or up to 3 divided doses, intravenous administration can include a continuous drip. Variations will necessarily occur depending on the weight and condition of the subject being treated and the particular route of administration chosen as will be known to those skilled in the art.

45 [0028] The following Examples illustrate the invention. The abbreviations used mean the following: GC=gas chromatography; MS=mass spectrometry; TLC=thin layer chromatography, HPLC = high performance liquid chromatography; LCMS = liquid chromatography mass spectrometry; and NMR = nuclear magnetic resonance.

50 Example 1

(1 α , 5 α , 6 α)-6-Acetamido-3-benzyl-3-azabicyclo[3.1.0]hexane

55 [0029] A 3-necked round bottom flask, equipped with a thermometer, a overhead stirrer and a condenser with nitrogen purge, was charged with 768 g of nitrocyclopropane, 5.75 L of isopropanol (7.5 volumes), 1.79 L of acetic acid (9.1 equivalents) and 1153 g of iron powder (6 equivalents). The reaction mixture was heated at 50°C until the reaction was completed by GC/MS analysis (about 6 hours). 448 mL of acetic anhydride (1.4 equivalents) was added and stirred at 50°C for 15 minutes before cooling. The reaction mixture was diluted with 8 L isopropanol (10.5 volumes) and stirred

for 30 minutes. The residual iron was filtered off and the cake washed with 11.25 L of isopropanol (15 volumes). The isopropanol solution was concentrated in vacuo to an oil, 18 L of dichloroethane (24 volumes) was added before bringing the pH to 12 with 8.8 L of 5% sodium hydroxide solution (about 12 volumes). The layers were separated and the separated organic layer was dried by magnesium sulfate. The resulting dark amber oil was treated with 7.5 L of hexanes (10 volumes) and granulated at 25°C before collecting the product as a white solid. Drying at 50°C under vacuum gave 610 g of the title compound (77 % yield). Analysis was done by GC/MS, NMR and TLC.

Example 2

(1 α , 5 α , 6 α)-6-Acetamido-3-azabicyclo[3.1.0]hexane

[0030] A Parr Bottle was charged with 150 g of the compound of Example 1, 112 mL of acetic acid (3 equivalents), 1.5 L of methanol (10 volumes) and 15 g of (10% by wt. 50% wet) Pd/C catalyst (0.1 equivalent). The bottle was purged with nitrogen and then brought to 50 psi pressure with hydrogen. The mixture was shaken for 48 hours and recharged with catalyst as necessary during the debenzylization reaction. After TLC indicated that the reaction was complete, the catalyst was filtered off, and the filtrate was concentrated in vacuo to an oil. 3 L of ethyl acetate (20 volumes) was added to the oil, and granulated for an hour. The solid was collected by filtration and dried under vacuum at 50°C to provide 107 g of the title compound (82 % yield) as the acetic acid salt.

Example 3

(1 α , 5 α , 6 α)-7-(6-acetamido-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, ethyl ester

[0031] A reaction flask was charged with 241.9 g of 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester, 151.6 g of the acetic acid salt of the compound of Example 2 (1.2 equivalents), 2661 mL of ethyl acetate (11 volumes) and 220 mL of triethylamine (2.5 equivalents). The mixture was heated at refluxing temperature under nitrogen for 6 hours monitored by HPLC or LCMS. After the reaction was completed, the reaction mixture was cooled to ambient temperature. Water (11 volumes) was added and the biphasic mixture was stirred for 17 hours. The white solid was collected by filtration, washed with 2661 mL of water (12 volumes) and oven dried at 50°C to provide 292 g of the title compound (95 % yield).

Example 4

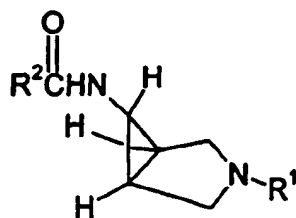
[0032] In a reaction flask, 220 g of the compound of Example 3, 1.76 L of n-butanol (8 volumes), 1.54 L of water (7 volumes) and 141 mL of 70% methanesulfonic acid (3.0 equivalents) were mixed. The mixture was heated at reflux for 21 hours, and the reaction was monitored by HPLC or LCMS. After complete reaction, the mixture was cooled to 50°C and filtered to make it speck-free. The filtrate was cooled to 0-5°C and granulated for 2 hours. The solid was collected by filtration, washed with 220 mL of water (1 volume) and 660 mL n-butanol (3 volumes). The wet cake was mixed with 660 mL of n-butanol (3 volumes), seeded with 0.1 gm of the desired polymorph and heated to 95-100°C. After complete polymorph conversion, in approximately 2 hours, the mixture was cooled to ambient temperature. The solid was filtered, washed with 100 mL of n-butanol (0.5 volumes) and dried in a nitrogen atmosphere to provide 200 g of (1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate (87% yield).

Example 5

[0033] 0.8 mL of methanesulfonic acid (2.7 equivalents) was added dropwise to a solution of 2.2 g of the compound of Example 3 in 10 mL of ethanol (4.5 volumes). The resulting reaction mixture was heated at refluxing temperature for 40 hours, monitored by GCMS. After the reaction was completed, it was diluted with ethyl acetate (20 mL) and washed with (3x 10ml) 1M sodium hydroxide solution. The organic layer was separated, dried over anhydrous magnesium sulphate and filtered. The filtrate was concentrated in vacuo to provide 1.37 g of (1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester, monomethanesulfonate (96% yield).

Claims

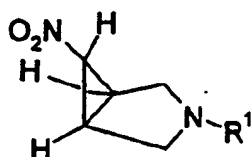
1. A process for preparing a compound of the formula



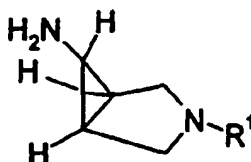
wherein

R¹ is benzyl, wherein the phenyl of the benzyl may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, and
R² is C₁-C₆ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, which comprises

(a) reducing a compound of the formula

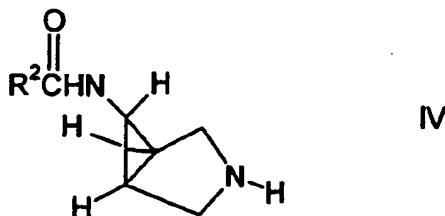


wherein R¹ is as defined above, in the presence of iron and a organic solvent under acidic conditions, and
(b) acylating the compound of formula III formed:



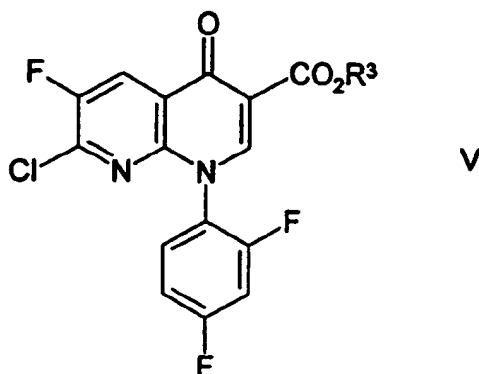
with an acylating agent of the formula R²C(O)X wherein R² is as defined above, and X is a leaving group.

2. A process according to claim 1 wherein the compound of the formula III formed in step (a) is not isolated before acylation step (b).
3. A process according to claim 1 or 2 wherein the compound of formula I wherein R¹ is as defined in claim 1, is subjected to debenzylation to form the compound of the formula

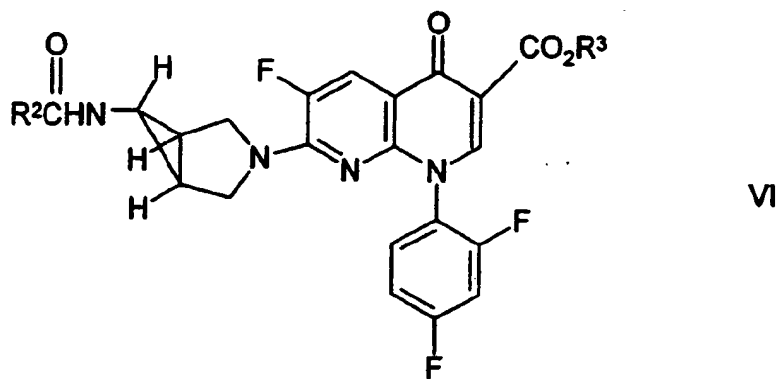


4. A process according to claim 3 wherein the debenzylation is by reaction with hydrogen and palladium catalyst in acetic acid and an organic solvent.

5. A process according to claim 3 or 4 further comprising reacting the compound of formula IV with a compound of the formula

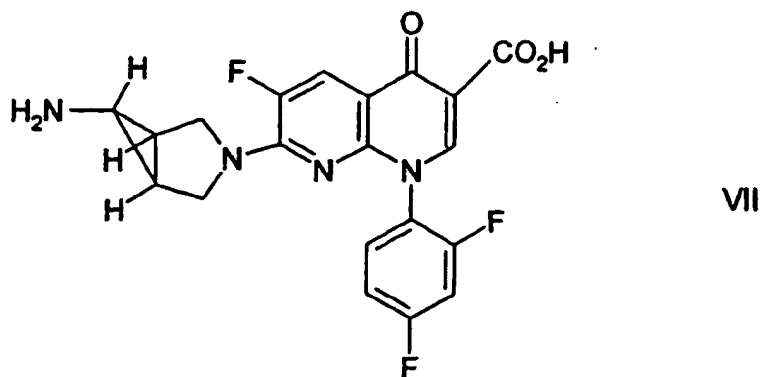


wherein R³ is C₁-C₆ alkyl, to form a compound of the formula

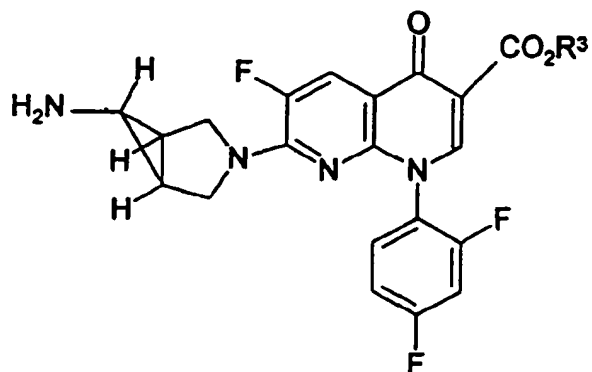


wherein R² is as defined in claim 1

6. A process according to claim 5 further comprising hydrolysis of the compound of formula VI with methanesulfonic acid, water and an organic solvent to form the monomethanesulfonic acid salt of the compound of the formula

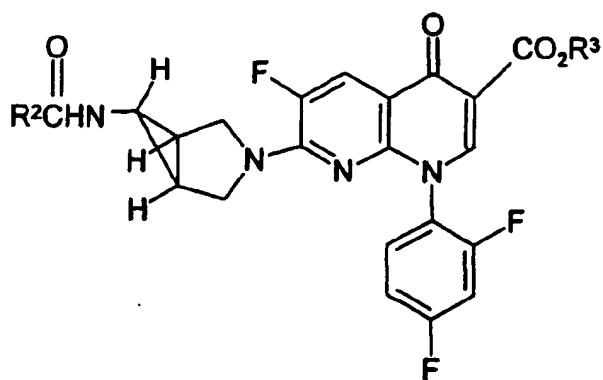


7. A process according to claim 5 or 6 further comprising hydrolysis of the compound of formula VI with methanesulfonic acid and R³OH wherein R³ is as defined in claim 5 to form the monomethanesulfonic acid salt of the compound of the formula



VIII

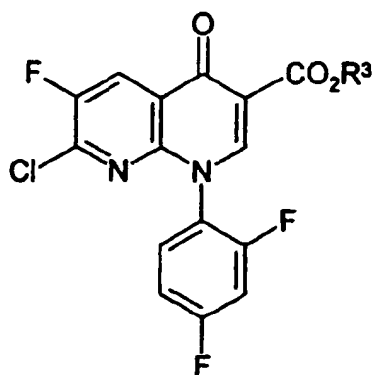
8. A process for the preparation of a compound of the formula



VI

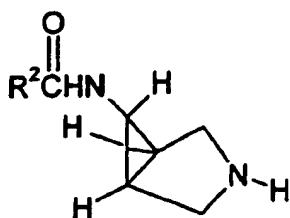
wherein R^2 is R^2 is C_1 - C_6 alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C_1 - C_6 alkyl, C_1 - C_6 alkoxy, halo, nitro, amino or trifluoromethyl, and

R^3 is C_1 - C_6 alkyl, which comprises reacting a compound of the formula



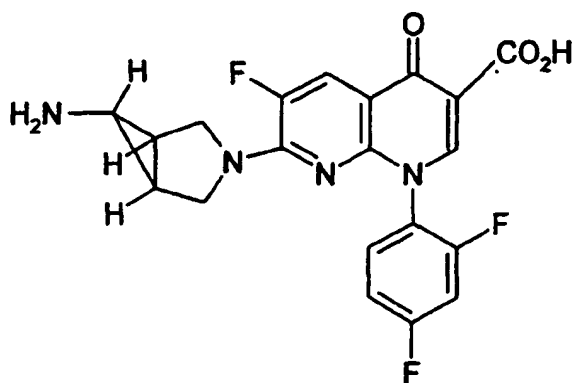
V

with a compound of the formula



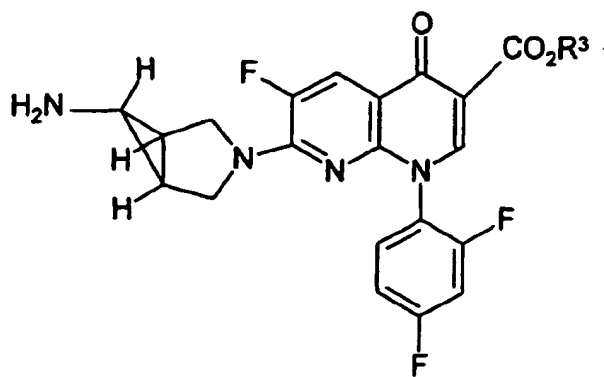
IV

9. A process according to claim 8, further comprising hydrolysis of the compound of formula VI with methanesulfonic acid, water and an organic solvent to form the monomethanesulfonic acid salt of the compound of the formula



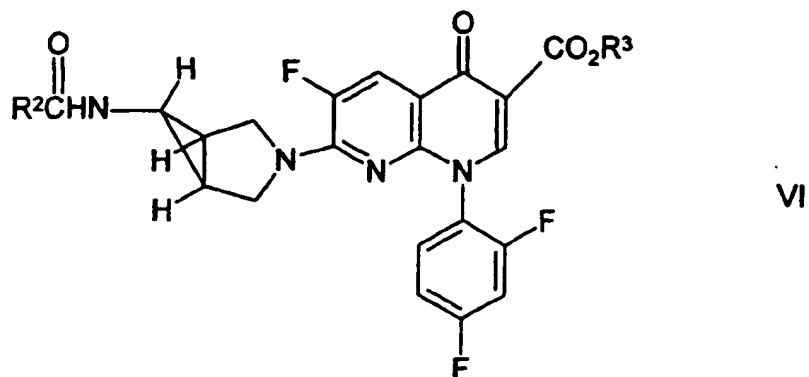
VII

10. A process according to claim 8, further comprising hydrolysis of the compound of formula VI with methanesulfonic acid and R^3OH wherein R^3 is as defined in claim 5 to form the monomethanesulfonic acid salt of the compound of the formula



VIII

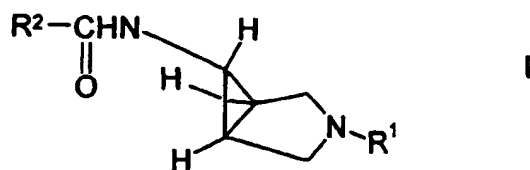
11. A compound of the formula



wherein

R² is C₁-C₆ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, and
R³ is C₁-C₆ alkyl.

12. A compound of the formula



wherein

R¹ is hydrogen or benzyl, wherein the phenyl of the benzyl may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, and
R² is C₁-C₆ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 99 30 0183

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Y	WO 93 18001 A (PFIZER) 16 September 1993 * page 5; claims 12-18; examples *	1-4,12	C07D209/52 C07D471/04 /(C07D471/04, 221:00,221:00)
Y	T.F. BRAISH ET AL.: "Construction of the (1-alpha,5-alpha,6-alpha)-6-amino-3-azabicyclo(3.1.0.)hexane ring system" SYNLETT., no. 11, 1996, pages 1100-1102, XP002100147 STUTTGART DE * the whole document *	1-4,12	
A	EP 0 413 455 A (PFIZER) 20 February 1991 * claims *	1-12	
D	& US 5 164 402 A		
D,A	US 5 475 116 A (BRIGHTY KATHERINE E ET AL) 12 December 1995 * the whole document *	1-12	
E	DE 197 33 439 A (BAYER AG) 4 February 1999 * the whole document *	1-12	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
			C07D
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 16 April 1999	Examiner Chouly, J
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p>			

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ON EUROPEAN PATENT APPLICATION NO.**

EP 99 30 0183

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16-04-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9318001 A	16-09-1993	US 5256791 A	26-10-1993
		AT 156480 T	15-08-1997
		AU 667872 B	18-04-1996
		CA 2131160 A,C	16-09-1993
		CN 1076440 A,B	22-09-1993
		DE 69312913 D	11-09-1997
		DE 69312913 T	20-11-1997
		DK 629189 T	08-12-1997
		EP 0629189 A	21-12-1994
		ES 2105217 T	16-10-1997
		FI 944013 A	01-09-1994
		GR 3024789 T	30-01-1998
		HU 70497 A	30-10-1995
		IL 104818 A	30-09-1997
		JP 2564247 B	18-12-1996
		JP 7500349 T	12-01-1995
		KR 135626 B	23-04-1998
		MX 9301138 A	31-01-1994
		NO 943243 A	01-09-1994
		NZ 246768 A	26-09-1995
		US 5298629 A	29-03-1994
		ZA 9301428 A	01-09-1994
EP 0413455 A	20-02-1991	WO 9102526 A	07-03-1991
		AT 124040 T	15-07-1995
		AU 623801 B	21-05-1992
		AU 6104290 A	21-02-1991
		CA 2023217 A,C	17-02-1991
		CA 2127561 A	17-02-1991
		CN 1049501 A,B	27-02-1991
		CZ 9004027 A	17-04-1996
		DD 298399 A	20-02-1992
		DE 69020262 D	27-07-1995
		DE 69020262 T	26-10-1995
		DK 413455 T	14-08-1995
		EG 19251 A	29-09-1994
		ES 2074131 T	01-09-1995
		FI 964520 A	11-11-1996
		GR 3017072 T	30-11-1995
		HK 1000207 A	06-02-1998
		IE 66202 B	13-12-1995
		IL 95331 A	31-07-1995
		JP 7149758 A	13-06-1995
		JP 8019099 B	28-02-1996
		JP 1975517 C	27-09-1995
		JP 3086875 A	11-04-1991

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**

EP 99 30 0183

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

16-04-1999

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0413455 A		JP 7002734 B	18-01-1995
		LU 90310 A	25-01-1999
		LU 90311 A	25-01-1999
		NO 300214 B	28-04-1997
		PL 166381 B	31-05-1995
		PT 94998 A, B	18-04-1991
		RU 2049777 C	10-12-1995
		US 5266569 A	30-11-1993
		US 5164402 A	17-11-1992
		US 5229396 A	20-07-1993
US 5475116 A	12-12-1995	NONE	
DE 19733439 A	04-02-1999	WO 9906368 A	11-02-1999

EPO FORM P469

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82